Background Recently, genome-wide association studies have revealed an association between single-nucleotide-polymorphisms (SNPs) in a genomic region containing the *ADAMTS7* (a disintegrin-like and metalloprotease with thrombospondin type 1 motif, 7) gene and susceptibility to coronary artery disease (CAD). However, it has remained unclear as to what biological mechanisms underlie this genetic association. We sought to assess possible functional effects of the non-synonymous SNP rs3825807, an adenine (A) to guanosine (G) change that results in a serine (Ser) to proline (Pro) substitution in the propeptide domain of the *ADAMTS7* protein, as the G allele of this SNP has been shown to be associated with reduced risk of CAD.

Methods and Results In a population-based, prospective study, we observed an inverse relationship between the rs3825807 G allele and prevalence and severity of carotid atherosclerosis determined by carotid ultrasound (Table 1). In immunohistochemical analyses of coronary and carotid atherosclerotic plaques, we detected the presence of *ADAMTS7* within and around smooth muscle cells in the plaques, particularly in areas near the border between the intima and media (Figure 1A). In studies of primary cultures of vascular smooth muscle cells (VSMCs) from different individuals, we found that VSMCs of the G/G genotype had a lower migratory ability than VSMCs of the A/A genotype (Figure 1B). We also found that conditioned media of VSMCs of the G/G genotype contained less of the cleaved form of thrombospondin-5 (Figure 1C),

Table 1 Carotid atherosclerosis in the Bruneck

	age/sex-adjusted model		multivariable model†	
	OR (95% CI)*	p-value	OR (95% CI)*	p-value
Presence of atherosclerosis in 1990	0.58 (0.35-0.96)	0.035	0.51 (0.31-0.84)	0.008
Presence of atherosclerosis in 1995	0.51 (0.32-0.82)	0.005	0.53 (0.31-0.90)	0.019
	β (95% CI)*	p-value	β (95% CI)*	p-value
Atherosclerosis score 1990	-0.43 (-0.77, -0.09)	0.013	-0.45 (-0.78, -0.11)	0.010
Atherosclerosis score 1995	-0.53 (-0.89, -0.16)	0.005	-0.50 (-0.86, -0.14)	0.006

*Odds ratios (OR) and regression coefficients (β) were derived from logistic and linear regression analyses respectively, comparing Pro/Pro versus Ser/Ser and Ser/Pro. †Multivariable analyses were performed with adjustment for variables correlated with atherosclerosis parameters in the Bruneck cohort.

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ADAMTS7 CLEAVAGE AND VASCULAR SMOOTH MUSCLE CELL MIGRATION IS AFFECTED BY A CORONARY ARTERY DISEASE ASSOCIATED VARIANT

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Figure 1

an ADAMTS7 substrate that had been shown to be produced by VSMCs and inhibit VSMC migration. Furthermore, we found that media conditioned by VSMCs of the G/G genotype had lower amounts of cleaved ADAMTS7 propeptide (Figure 1D). To further assess the effect of the Ser-to-Pro substitution on ADAMTS7 propeptide domain cleavage, we transfected cultured HEK293 cells with a plasmid for expressing either ADAMTS7-214Ser or ADAMTS7-214Pro, and then determined the relative amounts of the cleaved and uncleaved forms of ADAMTS7 propeptide in conditioned media. In these experiments, we found that media conditioned by cells transfected with the ADAMTS7-214Pro plasmid had less cleaved ADAMTS7 propeptide than media conditioned by cells transfected with the ADAMTS7-214Ser plasmid.

Conclusion The results of our study indicate that the CAD-associated SNP rs3825807 has a functional effect on ADAMTS7 maturation, thrombospondin-5 cleavage and VSMC migration, with the G allele associated with protection from atherosclerosis and CAD rendering a reduction in ADAMTS7 function.